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(54) Title: **New mixed derivatives of benzimidazole-arylpiperazine with affinity for 5-HT_{1A} and 5-HT_3 serotonergic receptors.**

(57) Summary:
New mixed derivatives of benzimidazole-arylpiperazine with affinity for 5-HT_{1A} and 5-HT_3 serotonergic receptors.
The present invention relates to novel compounds of general formula I, where X is an amide, thioamide, ester, ketone or hydroxymethyl group; R1 is hydrogen, halogen, alkyl or alkoxy; R2 is hydrogen, nitro or amino; R3 is hydrogen or alkyl; R4 is alkyl, aryl or heteroaryl; n is equal to 1-4; and the azabicyclic subunit is azabicyclo[x.y.z]alkyl.
Methods are described for the preparation of said compounds, which show an affinity for 5-HT_{1A} and 5-HT_3 serotonergic receptors, and are therefore of interest from a therapeutic standpoint in the treatment of central nervous system (CNS) disorders.

Azabicyclic subunit

[Image I]

DESCRIPTION

New mixed derivatives of benzimidazole-arylpiperazine with affinity for 5-HT_{1A} and 5-HT_3 serotonergic receptors.

The present invention relates to novel compounds of general formula I, where X is an amide, thioamide, ester, ketone or hydroxymethyl group; R^1 is hydrogen, halogen, alkyl or alkoxy; R^2 is hydrogen, nitro or amino; R^3 is hydrogen or alkyl; R^4 is alkyl, aryl or heteroaryl; n is equal to 1-4; and the azabicyclic subunit is azabicyclo[x.y.z]alkyl.

Methods are described for the preparation of said compounds, which show an affinity for 5-HT_{1A} and 5-HT_3 serotonergic receptors, and are therefore of interest from a therapeutic standpoint in the treatment of central nervous system (CNS) disorders.

Background

Within the heterogeneous superfamily of serotonergic receptors, the study of ligands with an affinity for the 5-HT_3 receptor is a great focus of current attention. In recent years, two areas have received particular attention: the anti-emetic action of 5-HT_3 antagonists in chemotherapy treatments with cytotoxic drugs (Bunce, K.; Tyers, M.; Beranek, P. *Trends Pharmacol. Sci.* 1991, 12, 46; Veyrat-Follet, C.; Farinotti, R.; Palmer, J.L. *Drugs* 1997, 53, 206) and their therapeutic application in the treatment of psychiatric disorders, such as anxiety, schizophrenia, psychosis, drug addiction and cognitive disorders (King, F. D.; Jones, B.J.; Sanger, G.J.; Eds. *5-Hydroxytryptamine-3 Receptor Antagonists*. CRC Press: Boca Raton, 1994; Greenshaw, A.J. *Trends Pharmacol. Sci.* 1993, 14, 265; Greenshaw, A.J.; Silverstone, P.H. *Drugs* 1997, 53, 20; Bloom, F.E.; Morales, M. *Neurochem. Res.* 1998, 23, 653). Recently, a new class of 5-HT_3 antagonists derived from benzimidazole has been identified (*WO97/35860*, Lopez-Rodriguez, M.L.; Morcillo, M.J.; Benhamu, B.; Riaguas, M.D. *Bioorg. Med. Chem. Lett.*, 1996. 6 (11). 1195), which have demonstrated anxiolytic activity in various pharmacological tests.

On the other hand, there are numerous works indicating that agents showing an affinity for the 5-HT_{1A} receptor are involved in the control of anxiety and depression (Gerhardt, C.C.; van Heerikhuizen, H. *Eur. J. Pharmacol.* 1997, 334, 1). Studies of structure-activity relationships conducted in recent years with new 5-HT_{1A} ligands derived from arylpiperazine have permitted the affinity for this receptor to be optimized (*WO96/06846*, Lopez-Rodriguez, M.L.; Morcillo, M.J.; Rosado, M.L.; Benhamu, B.; Sanz, A.M. *Bioorg. Med. Chem. Lett.*, 1996. 6, 689; Lopez-Rodriguez, M.L.; Rosado, M.L.; Benhamu, B.; Morcillo, M.J.; Sanz, A.M.; Orensanz, L.; Beneytez, M.E.; Fuentes, J.A.; Manzanares, J. *J. Med. Chem.*, 1996. 39, 4439; Beneytez, M.E.; Lopez-Rodriguez, M.L.; Rosado, M.L.; Morcillo, M.J.; Orensanz, L.; Fuentes, J.A.; Manzanares, J. *Eur. J. Pharmacol.* 1998, 344, 127). Based on these results and with the objective of obtaining new anxiolytics, we have designed and synthesized some new mixed derivatives of benzimidazole-arylpiperazine, incorporating the structural elements of the 5-HT_{1A} and 5-HT_3 pharmacophores into a single molecule. Some of these derivatives have turned out to be 5-HT_{1A}/5-HT_3 mixed ligands, which are an interesting alternative to the drugs currently marketed for the treatment of anxiety.

Description

The present invention relates to novel derivatives of benzimidazole-arylpiperazine, which have demonstrated an affinity for the serotonergic receptors 5-HT_{1A} and 5-HT_3.

The new compounds are represented by general formula I:

[Azabicyclic subunit]

[Image I]

where X is an amide, thioamide, ester, ketone or hydroxymethyl group; R^1 is hydrogen, halogen, alkyl or alkoxy; R^2 is hydrogen, nitro or amino; R^3 is hydrogen or alkyl; R^4 is alkyl, aryl or heteroaryl; n is equal to 1-4; and the azabicyclic subunit is azabicyclo[x.y.z]alkyl.

The compounds of general structure I have been synthesized by treatment of acid 1 with 1,1'-carbonyldiimidazole (CDI) and subsequent reaction of the intermediate imidazolide with the corresponding diamine or aminoalcohol, in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and anhydrous *N,N*-dimethylformamide (DMF) as the reaction solvent (Scheme 1). By treating the amides I (X = CONH) with Lawesson reagent, the corresponding thioamides were obtained (X = CSNH).

Scheme I

[Azabicyclo subunit]

[Image 1] **[Image I]**

Reagents: (a) CDI, DMF, N_2; (b) diamine or aminoalcohol, DBU, DMF, N_2.

Synthesis of the benzimidazolecarboxylic acids 1 (n = 1) was carried out by reaction of the corresponding hydroxymethyl derivative 2 with thionyl chloride, followed by acid hydrolysis and subsequent treatment with the corresponding piperazine, in the presence of triethylamine and acetonitrile as solvents (Scheme II).

Scheme II

[Image 2] **[Image]**

[Image 1]

Reagents: (a) $SOCl_2$; (b) HCl/H_2O; (c) HN **[Image]** $N\text{-}R^4/CH_3CN$, Et_3N.

The hydroxymethyl derivatives 2 are synthesized from 2-methyl-6-nitroaniline. For example, 2-hydroxymethyl-4-benzimidazolecarboxylic acid was obtained by following the synthetic route described by Jones, J.B.; Taylor, K.E. *Can. J. Chem.* 1977, 55, 1653.

The benzimidazolecarboxylic acids 1 (n = 2-4) were synthesized by reaction of a substituted piperazine with its corresponding halogenated acid in the presence of triethylamine and acetonitrile and subsequent condensation with 2,3-diaminobenzoic acid (Scheme III).

Scheme III

[Image]

Reagents: (a) Br [Image] COOH/ CH_3CN, Et_3N; (b) 2,3-diaminobenzoic acid/HCl. Δ.

The noncommercial arylpiperazines were obtained according to the methods described in the literature: Glennon, R.A.; Slusher, R.M.; Lyon, R.A.; Titeler, M.; McKenney, J.D. *J. Med. Chem.* 1986, 29, 2375; van Wijngaarden, I.; Kruse, C.G.; van der Heyden, J.A.M.; Tulp, M.T.M. *J. Med. Chem.* 1988, 31, 1934.

Methods for preparation of the inventions

Example 1

2-[[4-(o-methoxyphenyl)piperazine-1-yl]methyl]-4-benzimidazolecarboxylic acid, 1b

(a) *2-chloromethyl-4-benzimidazolecarboxylic acid.*

A solution of 2.0 g of 2-hydroxymethyl-4-benzimidazolecarboxylic acid in 45 mL of thionyl chloride is heated to 80°C for 2 hours (c.c.f.). After cooling, the thionyl chloride is removed under reduced pressure and the excess is eliminated through four successive co-distillations with toluene. The residue is then dissolved in 20 mL of dilute hydrochloric acid and heated to reflux for 15 minutes. After removal of the solvent under reduced pressure, 2.0 g (95%) of 2-chloromethyl-4-benzimidazolecarboxylic acid are obtained. M.p. 232-234°C (methanol/ethyl ether).

(b) *2-[[4-(o-methoxyphenyl)piperazine-1-yl]methyl]-4-benzimidazolecarboxylic acid.*

1.1 mL of triethylamine is added to a suspension of 0.74 g of 2-chloromethyl-4-benzimidazolecarboxylic acid, 0.96 g of 1-(*o*-methoxyphenyl)piperazine and 6 ml of acetonitrile, and the reaction mixture is heated to 60°C for 20-24 hours (c.c.f.). After cooling, the solvent is removed under reduced pressure, the residue is diluted in water and extracted with methylene chloride (3 X 30 mL). The organic extracts are dried over anhydrous sodium sulfate and the solvent is removed under reduced pressure. A solid is obtained, which is purified by column chromatography on Silica gel (methylene chloride/methanol/ammonia), yielding 0.72 g (66%) of 2-[[4-(*o*-methoxyphenyl)piperazine-1-yl]methyl]-4-benzimidazolecarboxylic acid. M.p. 186-187°C (methanol/ethyl ether).

Analogously, the following compounds were prepared:

2-[(4-phenylpiperazine-1-yl)methyl]-4-benzimidazolecarboxylic acid. M.p. 272-273°C (methanol/ethyl ether), 1a.

2-[[4-(*o*-ethoxyphenyl)piperazine-1-yl]methyl]-4-benzimidazolecarboxylic acid. M.p. 145-147°C (methanol/ethyl ether), 1c.

2-[[4-(*m*-chlorophenyl)piperazine-1-yl]methyl]-4-benzimidazolecarboxylic acid. M.p. 247-248°C (methanol/ethyl ether), 1d.

2-[[4-(*m*-(trifluoromethyl)phenyl)piperazine-1-yl]methyl]-4-benzimidazolecarboxylic acid. M.p. 263-264°C (methanol), 1e.

2-[[4-(1-naphthyl)piperazine-1-yl]methyl]-4-benzimidazolecarboxylic acid. M.p. 236-238°C (methanol), 1f.

2-[[4-(2,3-dihydro-1,4-benzodioxane-5-yl)piperazine-1-yl]methyl]-4-benzimidazolecarboxylic acid. M.p. 186-187°C (ethanol/ethyl ether), 1g.

Example 2

2-[4-[4-(o-methoxyphenyl)piperazine-1-yl]butyl]-4-benzimidazolecarboxylic acid, Ih.

(a) *δ-[4-(o-methoxyphenyl)piperazine-1-yl]valeric acid.*

10.9 mL of triethylamine is added to a suspension of 5.3 g δ-bromovaleric acid, 9.4 g of 1-(*o*-methoxyphenyl)piperazine and 62 ml of acetonitrile, and the reaction mixture is heated to 60°C for 26 hours (c.c.f.). After cooling, the solvent is removed under reduced pressure, the residue is diluted in water and extracted with methylene chloride (3 X 200 mL). The organic extracts are dried over anhydrous sodium sulfate and the solvent is removed under reduced pressure. A solid is obtained, which is purified by column chromatography on Silica gel (methylene chloride/methanol/ammonia), yielding 1.8 g (21%) of δ-[4-(*o*-methoxyphenyl)piperazine-1-yl]valeric acid. M.p. 134-136°C (methanol/ethyl ether).

(b) *2-[4-[4-(o-methoxyphenyl)piperazine-1-yl]butyl]-4-benzimidazolecarboxylic acid.*

A solution of 0.62 g of δ-[4-(*o*-methoxyphenyl)piperazine-1-yl]valeric acid and 0.48 g of 2,3-diaminobenzoic acid in 6 mL of 4N hydrochloric acid is refluxed for 6 hours (c.c.f.). After cooling to ambient temperature, 25 mL of 10% sodium bicarbonate is added and the aqueous phase is extracted with chloroform (3 x 50 mL). The organic extracts are dried over sodium sulfate, the solvent is removed under reduced pressure and the resulting residue is purified by column chromatography on Silica gel (chloroform/ethane/ammonia), yielding 0.21 g (24%) of 2-[4-[4-(o-methoxyphenyl)piperazine-1-yl]butyl]-4-benzimidazolecarboxylic acid. M.p. 105-107°C (chloroform/ethyl ether).

Example 3

N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-[[4-(o-methoxyphenyl)piperazine-1-yl]methyl]-4-benzimidazolecarboxamide, Ib.

0.40 g of 1,1'-carbonyldiimidazole is added, in a nitrogen atmosphere, to a solution of 0.91 g of 1b in anhydrous *N,N*-dimethylformamide (2.5 mL) and the resulting solution is heated to 40°C for 1 hour. A solution of 0.47 g of (±)-3-aminoquinuclidine and 0.38 g of 1,8-diazabicyclo[5.4.0]undec-7-ene in *N,N*-dimethylformamide (5 mL) is added dropwise. The reaction mixture is heated to 50°C for 20-24 hours in a nitrogen atmosphere. The solvent is evaporated under reduced pressure and the resulting oil is dissolved in 25 mL of chloroform, washed first with 10 mL of water and subsequently with 10 mL of 20% aqueous potassium carbonate. The organic extracts are dried over Na_2SO_4, the solvent is removed under reduced pressure and the residue is purified by column chromatography on Silica gel (methylene chloride/ethanol/ammonia), yielding 0.75 g (64%) of Ib. M.p. 122-123°C (acetone).

Analogously, the following compounds were prepared:

N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-[(4-phenylpiperazine-1-yl]methyl]-4-benzimidazolecarboxamide, M.p. 146-147°C (chloroform/ethyl ether), Ia.

N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-[[4-(*o*-ethoxyphenyl)piperazine-1-yl]methyl]-4-benzimidazolecarboxamide, M.p. 143-144°C (chloroform/ethyl acetate), Ic.

N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-[[4-(*m*-chlorophenyl)piperazine-1-yl]methyl]-4-benzimidazolecarboxamide, M.p. 182-183°C (acetone), Id.

N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-[[4-(*m*-(trifluoromethyl)phenyl)piperazine-1-yl]methyl]-4-benzimidazolecarboxamide, M.p. 173-175°C (chloroform), Ie.

N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-[[4-(1-naphthyl)piperazine-1-yl]methyl]-4-benzimidazolecarboxamide, M.p. 215-217°C (chloroform), If.

N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-[[4-(2,3-dihydro-1,4-benzodioxane-5-yl)piperazine-1-yl]methyl]-4-benzimidazolecarboxamide, M.p. 196-197°C (chloroform/ethyl acetate), Ig.

N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-[4-[4-(*o*-methoxyphenyl)piperazine-1-yl]butyl]-4-benzimidazolecarboxamide, M.p. 81-83°C (chloroform/ethyl ether), Ih.

Example 4

Affinity values (K_i) for 5-HT_{1A} serotonergic receptors

The affinities of some of the compounds of general structure I for the 5-HT_{1A} serotonergic receptors in the cerebral cortex membranes of rats, *in vitro*, were determined with radioligand displacement techniques using [^{3}H]-8-OH-DPAT [8-hydroxy-2-(dipropylamine)tetraline] as a selective ligand.

Procedure

The experimental animals, male albino rats (*Rattus norvegicus albinos*) of the Sprague-Dawley race, weighing approximately 200 g., are sacrificed by decapitation. The brains are quickly removed and frozen in liquid nitrogen. The tissue is stored at -80°C before use.

We followed the procedure used by Clark, R.D. *et al., J. Med. Chem.* 1990. 33, 633, which is described below.

The cerebral cortex is homogenized in 10 volumes of 50 mM Tris-HCl buffer, pH 7.7 at 4°C and centrifuged at 28,000 times g for 15 min. at 4°C. The supernatant is discarded and the resuspended sediment is incubated at 37°C for 10 min. The membranes are centrifuged again and the sediment is resuspended in 10 volumes of Tris-HCl buffer with 5 mM $MgSO_4$ and 0.5 mM EDTA (pH 7.4 at 25°C). 100 µl membrane fractions from the final membrane suspension (5 mg/mL of protein) are incubated for 15 min. at 37°C with 0.6 nM [^{3}H]-8-OH-DPAT, in the presence or absence of a concentration interval (10^{-5} – 10^{-10} M) of the test compound in a final volume of 1.1 mL of 50 mM Tris-HCl buffer with clonidine 10 nM and prazosin 30 nM at pH 7.4. Nonspecific binding is determined with serotonin 10 µM. The bound and free radioligands are separated by vacuum filtration with Whatman GF/C filters washed twice with 4 mL of 50 mM Tris-HCl buffer, pH 7.4 at 4°C. Scintillation fluid (Ecolite) 4 mL is added and the radioactivity present in the membranes is counted by liquid scintillation spectrometry

In the case of active compounds (those whose inhibition is >55% at a concentration of 10^{-6} M), the IC_{50} is determined through nonlinear regression of the displacement curve obtained for 6 different concentrations of the compound (10^{-5} – 10^{-10} M), using the equation $\%EU = 100(1 - C^b)/(IC_{50}{}^b + C^b)$. The conversion of IC_{50} to K_i is carried out using the equation $K_i = IC_{50}/(1+L/K_D)$ (Cheng, Y.C.; Prusoff, W.H. *Biochem. Pharmacol.* 1973, 22, 3099), where L is the concentration and K_D is the dissociation constant of the radioligand used.

The results obtained are shown in Table 1.

Example 5

Affinity values (K_i) for 5-HT_3 serotonergic receptors

The affinities of some of the compounds of general structure I for the 5-HT_3 serotonergic receptors in the cerebral cortex membranes of rats, *in vitro*, were determined with radioligand displacement techniques using [^{3}H]LY 278584 ([^{3}H]-1-methyl-*N*-(*endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1 *H*-3-indazolecarboxamide) as a selective ligand.

Procedure

The same procedure was used to obtain rat brains as was described for the 5-HT_{1A} receptor.

We followed the procedure used by Wong, D.T. et al., *Eur. J. Pharmacol.* 1989. 166,107, which is described below.

The cerebral cortex is homogenized in 9 volumes of 0.32 M saccharose and centrifuged at 1,000 times g for 10 min. at 4°C. The sediment is washed twice by resuspension in 60 volumes of 50 nM Tris-HO buffer, pH 7.4 at 4°C. After the second washing, the resuspended sediment is incubated at 37°C for 10 min. The membranes are centrifuged again under the same conditions and the sediment is resuspended in 2.75 volumes of incubation buffer, composed of 50 mM Tris-HCl, 10 µM pargiline, 0.6 mM ascorbic acid and 5 mM $CaCl_2$ (pH 7.4 at 25°C).

100 µl fractions (approximately 2 mg/mL of protein) of the final membrane suspension are incubated for 30 min. at 25°C with 0.7 nM [^{3}H]LY 278584, in the presence or absence of a concentration interval (10^{-5} – 10^{-10} M) of the test compound in a final volume of 2 mL of incubation buffer. Nonspecific binding is determined with 10 µM 5-HT. The bound and free radioligands are separated by vacuum filtration with Whatman GF/C filters washed twice with 4 mL of 50 mM Tris-HCl buffer, pH 7.4 at 4°C. Scintillation fluid (Ecolite) 4 mL is added and the radioactivity present in the membranes is counted by liquid scintillation spectrometry

In the case of active compounds (those whose inhibition is >55% at a concentration of 10^{-6} DI), the IC_{50} is determined in the same manner as was described for 5-HT_{1A} receptor.

The results obtained are shown in Table 1.

TABLE 1

Affinity[a] data for I compounds

Compound	K_i ∀ E.E. (nM)	
	5-HT_3	5-HT_{1A}
Ia	23.1 ± 1.5	>10000
Ib	10.3 ± 1.1	150 ∀ 33
Ic	27.2 ± 0.9	18.0 ± 1.7
Id	18.3 ± 0.4	>10000
Ie	23.9 ± 2.9	>10000
If	24.4 ∀ 0.5	467 ∀ 14
Ig	32.5 ± 5.3	>10000
Ih	17.6 ± 0.1	6.7 ± 0.6

[a] The data represent the mean value and standard error of K_i for two to four experiments done in triplicate.

CLAIMS

1. Compounds of general formula I or pharmaceutically acceptable salts,

[Azabicyclic subunit]

[Image I]

wherein X is an amide, thioamide, ester, ketone or hydroxymethyl group; R^1 is hydrogen, halogen, alkyl or alkoxy; R^2 is hydrogen, nitro or amino; R^3 is hydrogen or alkyl; R^4 is alkyl, aryl or heteroaryl; n is equal to 1-4; and the azabicyclic subunit is azabicyclo[x.y.z]alkyl.

2. A compound according to claim 1, where X is an amide group; R^1, R^2 and R^3 are hydrogens; R^4 is phenyl, *o*-methoxyphenyl, *o*-ethoxyphenyl, *m*-chlorophenyl, *m*-trifluoromethylphenyl, naphthyl or benzodioxanyl; n is 1 and the azabicyclic subunit is 1-azabicyclo[2.2.2]oct-3-yl.

3. A compound according to claim 1, where X is an ester group; R^1, R^2 and R^3 are hydrogens; R^4 is phenyl, *o*-methoxyphenyl, *o*-ethoxyphenyl, *m*-chlorophenyl, *m*-trifluoromethylphenyl, naphthyl or benzodioxanyl; n is 1 and the azabicyclic subunit is 1-azabicyclo[2.2.2]oct-3-yl.

4. A compound according to claim 1, where X is a thioamide group; R^1, R^2 and R^3 are hydrogens; R^4 is phenyl, *o*-methoxyphenyl, *o*-ethoxyphenyl, *m*-chlorophenyl, *m*-trifluoromethylphenyl, naphthyl or benzodioxanyl; n is 1 and the azabicyclic subunit is 1-azabicyclo[2.2.2]oct-3-yl.

5. A compound according to claim 1, where X is a carbonyl group; R^1, R^2 and R^3 are hydrogens; R^4 is phenyl, *o*-methoxyphenyl, *o*-ethoxyphenyl, *m*-chlorophenyl, *m*-trifluoromethylphenyl, naphthyl or benzodioxanyl; n is 1 and the azabicyclic subunit is 1-azabicyclo[2.2.2]oct-3-yl.

6. A compound according to claim 1, where X is a hydroxymethyl group; R^1, R^2 and R^3 are hydrogens; R^4 is phenyl, *o*-methoxyphenyl, *o*-ethoxyphenyl, *m*-chlorophenyl, *m*-trifluoromethylphenyl, naphthyl or benzodioxanyl; n is 1 and the azabicyclic subunit is 1-azabicyclo[2.2.2]oct-3-yl.

7. A compound according to claim 1, where X is an amide group; R^1, R^2 and R^3 are hydrogens; R^4 is *o*-methoxyphenyl; n is 4 and the azabicyclic subunit is 1-azabicyclo[2.2.2]oct-3-yl.

8. A procedure for obtaining compounds of general formula I, characterized by the reaction of carboxylic acids 1 with the (±)-3-aminoquinuclidine in the presence of 1,1'-carbonyldiimidazole (CDI) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in anhydrous *N,N*-dimethylformamide (DMF) as the solvent.

9. A procedure for obtaining benzimidazolecarboxylic acids 1 (n = 1) by reaction of the corresponding hydroxymethyl derivative 2 with thionyl chloride, followed by acid hydrolysis and subsequent treatment with the corresponding piperazine, in the presence of triethylamine and acetonitrile as the solvent.

10. A procedure for obtaining benzimidazolecarboxylic acids 1 (n = 2-4) by reaction of a substituted piperazine with the corresponding halogenated acid in the presence of triethylamine and acetonitrile, and subsequent condensation with the 2,3-diaminobenzoic acid.

11. Compounds of general structure I for use as drugs.

12. Use of the compounds of general formula I for the preparation of drugs intended for the treatment of central nervous system disorders.

(19) [Image] SPANISH OFFICE OF PATENTS AND TRADEMARKS

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RELEVANT DOCUMENTS

Category	Cited documents	Affected Claims
A	WO 9735860 A (UNIV. COMPLUTENSE DE MADRID), 10-02-1997, entire document.	1-8.11
A	WO 9606846 A (UNIV. COMPLUTENSE DE MADRID), 03-07-1996, entire document.	1-8.11
A	EP 628549 A (SPANISH CHEMICAL AND PHARMACEUTICAL PRODUCTS COMPANY, INC.) 12-14-1994, entire document.	1-10
A	ES 2094690 A (UNIV. COMPLUTENSE DE MADRID), 01-16-1997, entire document.	1-10
A	WO 9824771 A (FUJISAWA PHARMACEUTICAL CO) 06-11-1998, composed with RN 208774-04-3, RN 200772-69-4, RN 208771-87-3, RN 208769-14-6.	1-11

Category of the cited documents

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